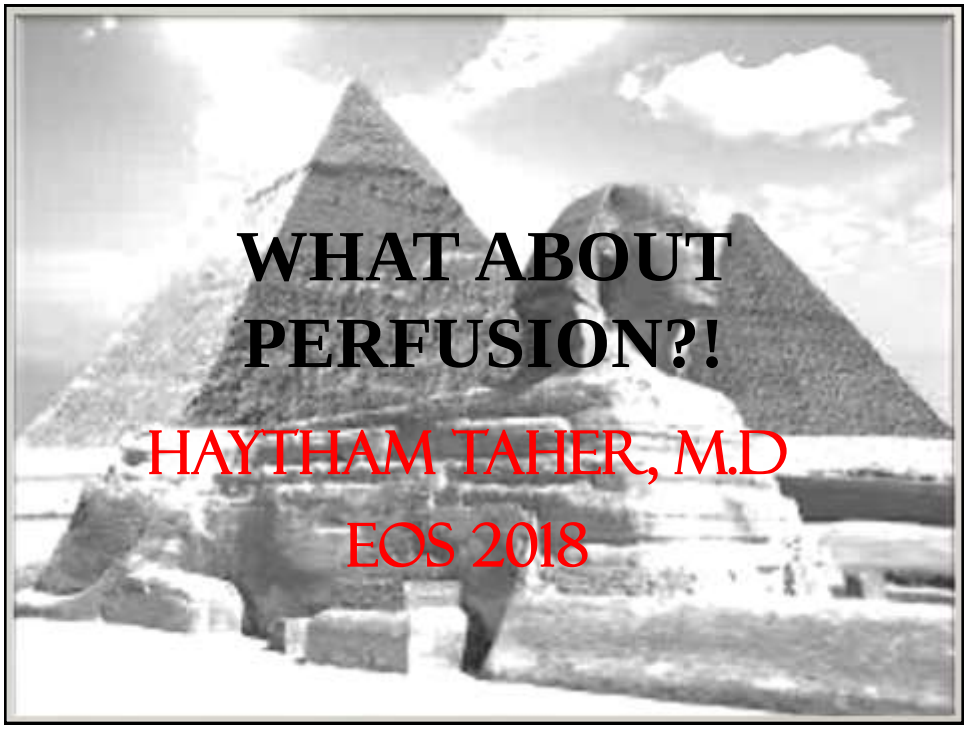

WHAT ABOUT PERFUSION?!

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I have no financial disclosure

Could I inject Anti-VEGF in cases with peripheral retinal ischemia?

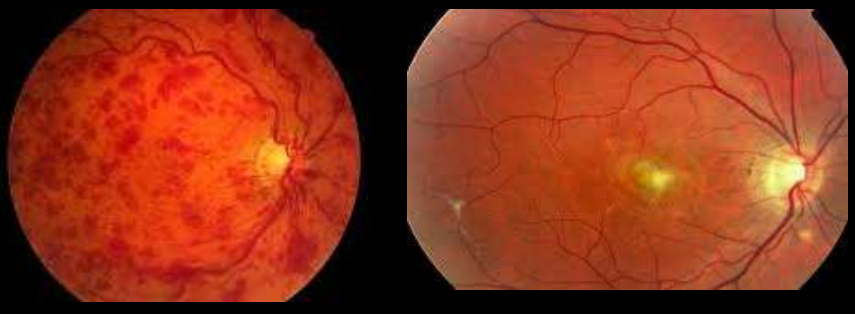
YES NO

Could intra-vitreal Anti-VEGF replace PRP in some cases?

YES NO

- Intravitreal injection is an excellent method for delivering drugs for multiple vitreoretinal diseases, the incidences of which are increasing globally every year.

- Multiple vitreoretinal diseases such as CNV, diabetic macular edema, and macular edema due to retinal vein occlusion are treated with intravitreal injection . Thus, expansion of the use of intravitreal injections is expected.



IN DIABETES MELLITUS

High blood glucose and advanced glycosylation end products

1) constriction and leakage of retinal vasculature.
2) thickening of the basement membrane
3) pericyte apoptosis.

ischemia, promoting a cascade of molecular processes including upregulation of hypoxia inducible factor-1, which in turn upregulates cytokines and growth factors, including vascular endothelial growth factor (VEGF),

In support of the clinical evidence, studies in animal models indicate a correlative role of VEGF in diabetic retinopathy.

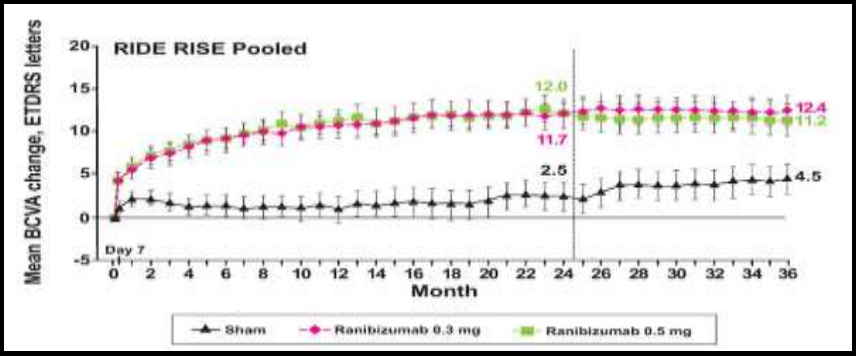
Injection of VEGF into vitreous fluid induces lesions consistent with diabetic retinopathy.

Neutralizing VEGF in diabetic rats inhibits blood–retinal barrier breakdown in a dose-dependent manner .

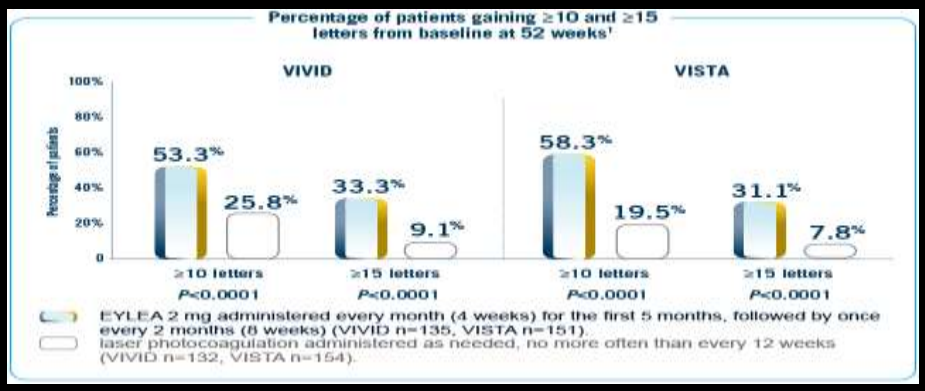
These findings indicate that VEGF is a major contributor to diabetic retinopathy and diabetic macular edema.

- Major clinical trials have demonstrated that anti-VEGF therapies improve vision

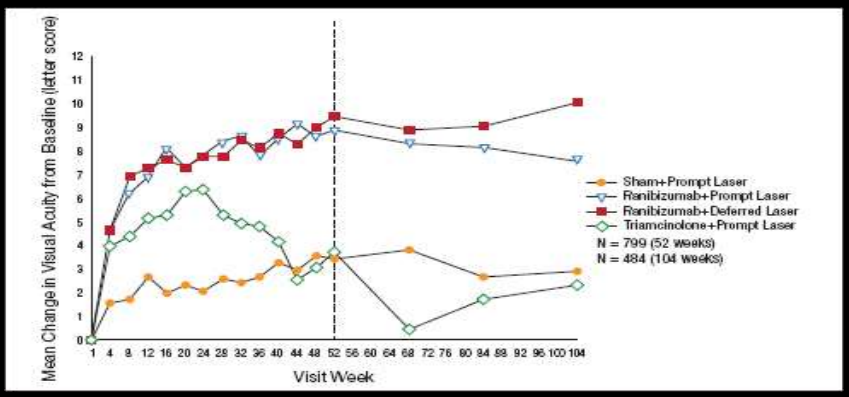
- The RISE and RIDE trials demonstrated that intravitreal injection of ranibizumab 0.3 and 0.5 mg (Lucentis, Hoffman-La Roche Ltd, Basel, Switzerland), a monoclonal antibody against VEGF-A, as compared with sham injections, improved all measures of vision assessed in the trials.



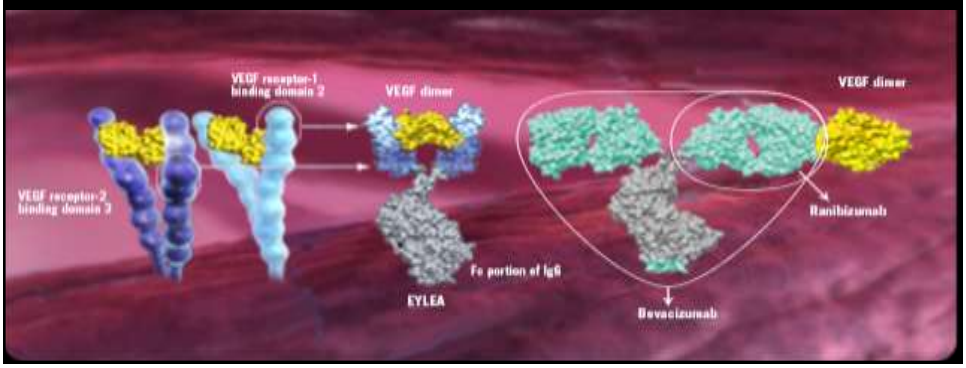
- The VIVID and VISTA trials demonstrated that intravitreal aflibercept 2 mg (Eylea, Regeneron Pharmaceuticals, Inc, Tarrytown, NY, USA) therapy resulted in greater gains and fewer losses in visual acuity when compared with laser



- In The Diabetic Retinopathy Clinical Research Network's (DRCR.net) Protocol I, treatment with ranibizumab plus prompt or deferred laser improved patient visual acuity, as compared with sham injections and laser.



- These and other studies have established anti-VEGF intravitreal injections as the standard of care for the treatment of diabetic macular edema.

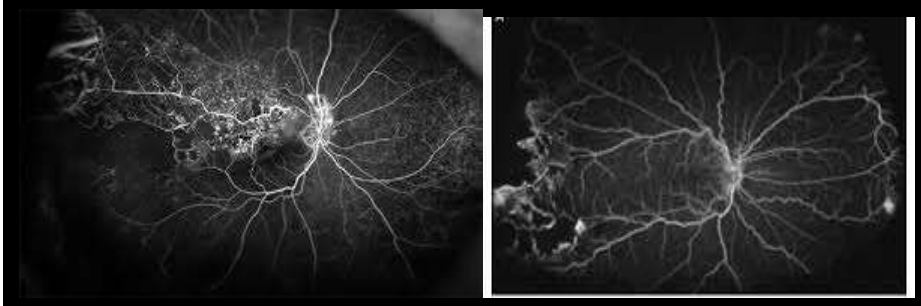


- In addition to improvement of visual acuity and reduction of diabetic macular edema, studies have shown that anti-VEGF therapies normalize blood vessels on color fundus photographs.

- Analyses of photographs obtained in RISE and RIDE demonstrated that patients receiving intravitreal ranibizumab were more likely to have ≥2-step or ≥3-step improvement in Diabetic Retinopathy Severity Scale score than patients receiving sham injections

- In VIVID and VISTA, a greater proportion of eyes treated with intravitreal aflibercept had ≥2-step improvement in Diabetic Retinopathy Severity Scale score

- Development of ***ultra-widefield fluorescein angiography*** (UWFA) has expanded visualization of the retina to 200° of the retina from 75° on the 7SF protocol, enabling more thorough assessment of peripheral nonperfusion and neovascularization



- A study Was done by Ariana Levin, et al and published in 2017 to report peripheral reperfusion of ischemic areas of the retina on ultra-wide field fluorescein angiography (UWFA) following anti-vascular endothelial growth factor (VEGF) intravitreal injections in patients treated for diabetic retinopathy.

- This study was a retrospective review of 16 eyes with diabetic retinopathy, who received anti-VEGF intravitreal injections and underwent pre- and post injection UWFA.
- The main outcome measured was the presence of reperfusion in post injection UWFA images in areas of the retina that demonstrated ***non perfusion*** in pre injection images.

- **Retinal non perfusion** is defined as at least five disc areas of hypofluorescence (representing retinal non perfusion or capillary dropout) on UWFA

The inclusion criteria were:

- Diagnosis of diabetic retinopathy (non-proliferative or proliferative diabetic retinopathy)
- Treatment with at least one anti-VEGF injections in the study eye (ranibizumab 0.3 mg, aflibercept 2 mg, or bevacizumab 1.25 mg)
- Pre- and post-injection UWFA imaging available, with the post-injection UWFA being within 5 months of the last intravitreal anti-VEGF injection in the study eye.

The exclusion criteria were:

- History of intravitreal anti-VEGF therapy before the pre injection UWFA
- Poor quality of imaging due to media opacity
- Concurrent nondiabetic retinal vascular disease (retinal artery occlusion, retinal vein occlusion),
- Absence of retinal nonperfusion on pre injection UWFA.

- Pairs of pre- and post injection UWFA images were graded for reperfusion as:

❑ 1= reperfusion present in post injection image compared side-by-side with pre injection image

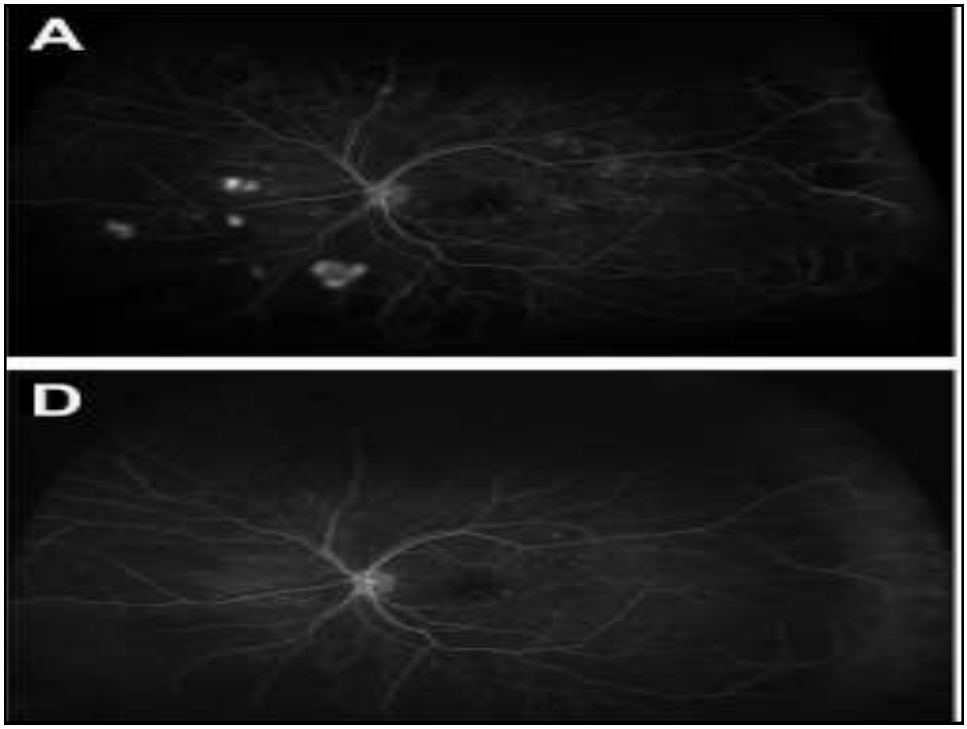
❑ 0= no reperfusion by 2 independent graders

- Reperfusion was *confirmed quantitatively using Image J software.*
- Quantitative analysis prevented bias resulting from recognition of an image as pre- or post-injection and from the assessment of an area of reperfusion as darker or lighter based on the brightness of surrounding vasculature.

This Study shows:

- Twelve out of 16 eyes (75%) demonstrated reperfusion **both qualitatively and quantitatively** on UWFA following anti-VEGF therapy

- Eleven eyes who reperfused received only ranibizumab injections, 1 received only bevacizumab injections, and the mean number of injections per eye was 3 (range: 1–6)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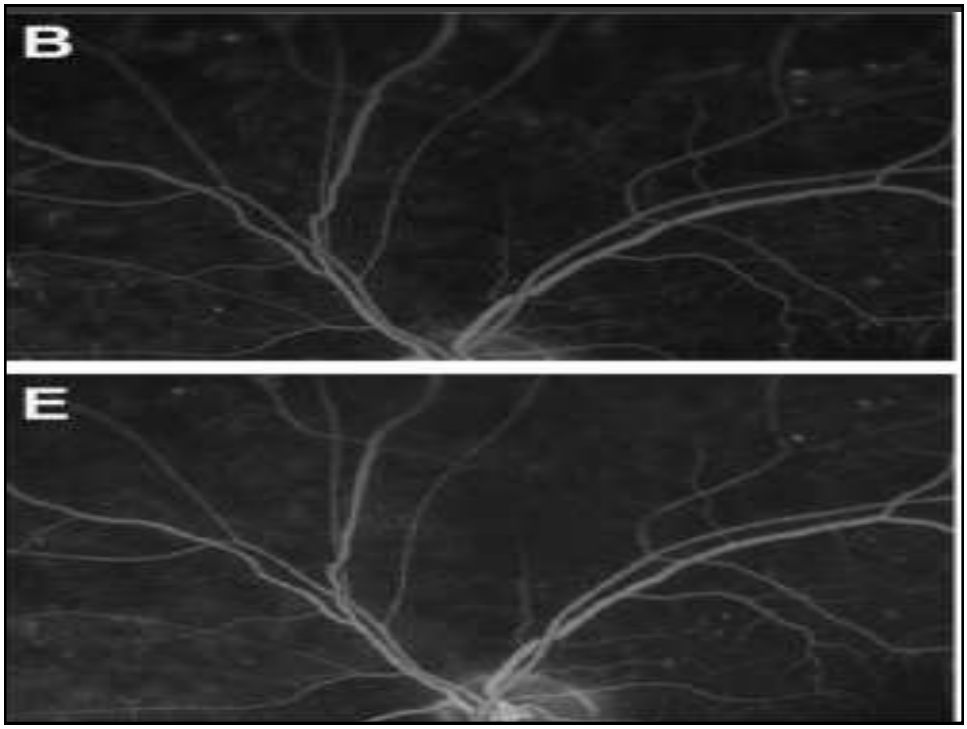
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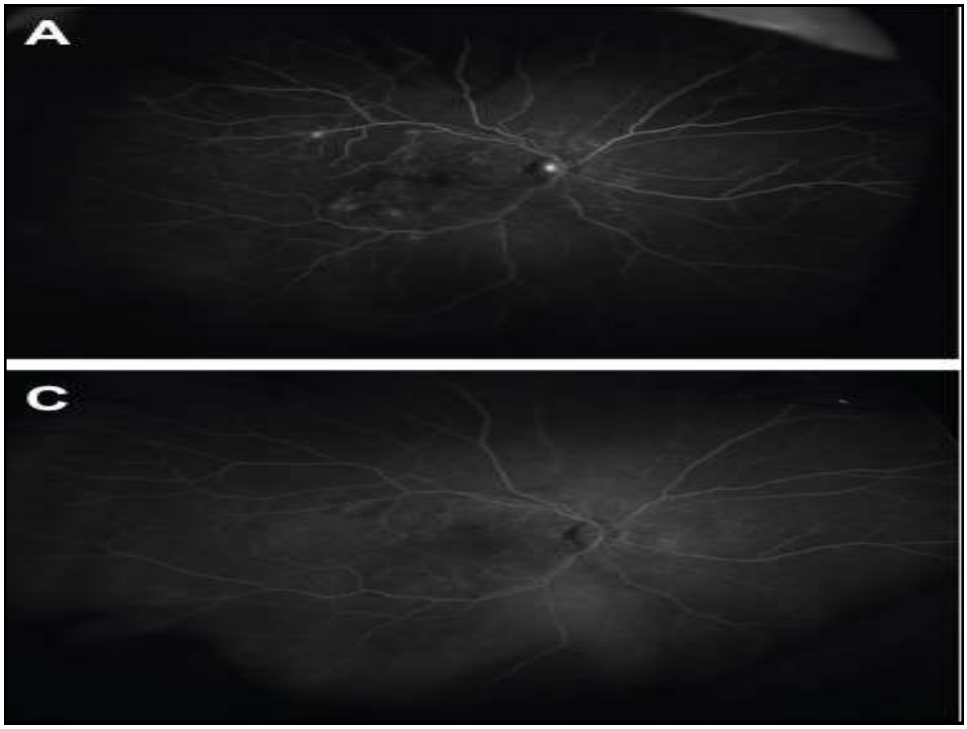

Variable	Positive reperfusion (n=12)	Negative reperfusion (n=4)
Drug (n)[‡]		
Ranibizumab	11	2
Bevacizumab	1	2
Aflibercept	0	1
No injections		
Mean	3	7.25
Range	1.0–6.0	5.0–14.0
Time between last injection and postinjection UWFA (days)		
Mean	67	42
Range	21.0–144.0	21.0–70.0
Time of FA after dye injected (seconds)		
Mean	72	58
Range	38.0–110.0	38.0–91.0
Time difference between pre- and postinjection images evaluated (seconds)		
Mean	4.5	15.5
Range	0.0–28.0	1.0–31.0

- In this small retrospective case series, they demonstrate that treatment of diabetic retinopathy with anti-VEGF injections has the potential to reverse retinal ischemia as noted on UWFA.
- These findings suggest that areas of ischemia on UWFA can possess viable, salvageable tissue with the potential to reperfuse.

- Some eyes demonstrated expansive reperfusion, while other eyes reperfused in only limited areas of the retina, while some eyes did not reperfuse at all.

- One possibility is that ischemic areas that do not reperfuse following anti-VEGF injections might be completely infarcted or might involve living tissue that is not responsive to the given doses of anti-VEGF injections.

- One patient who did not reperfuse had expansive scarring from pan-retinal photocoagulation that may have prevented reperfusion or detection of reperfusion

- The exact molecular mechanism by which anti-VEGF therapies normalize retinal blood vessels remains unknown, but studies of other retinal diseases and extensive studies of anti-VEGF effects on tumors might give insight into the role of anti-VEGF therapy in the retina.

- Another prior study demonstrated reversal of retinal non perfusion in eyes treated with anti-VEGF agents for retinal vein occlusion.

- The authors of the study hypothesized that anti-VEGF agents interrupt a positive feedback loop in which injury induces VEGF signaling, resulting in further injury

- They defined reperfusion as either neovascularization or recanalization, and found recanalization in one-third of eyes

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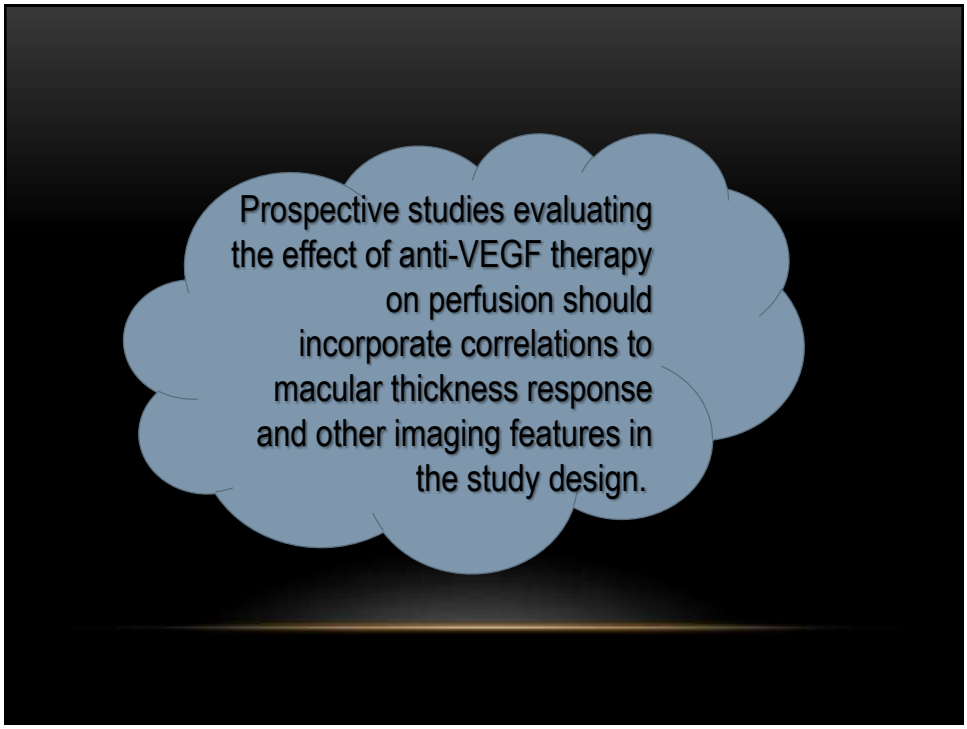
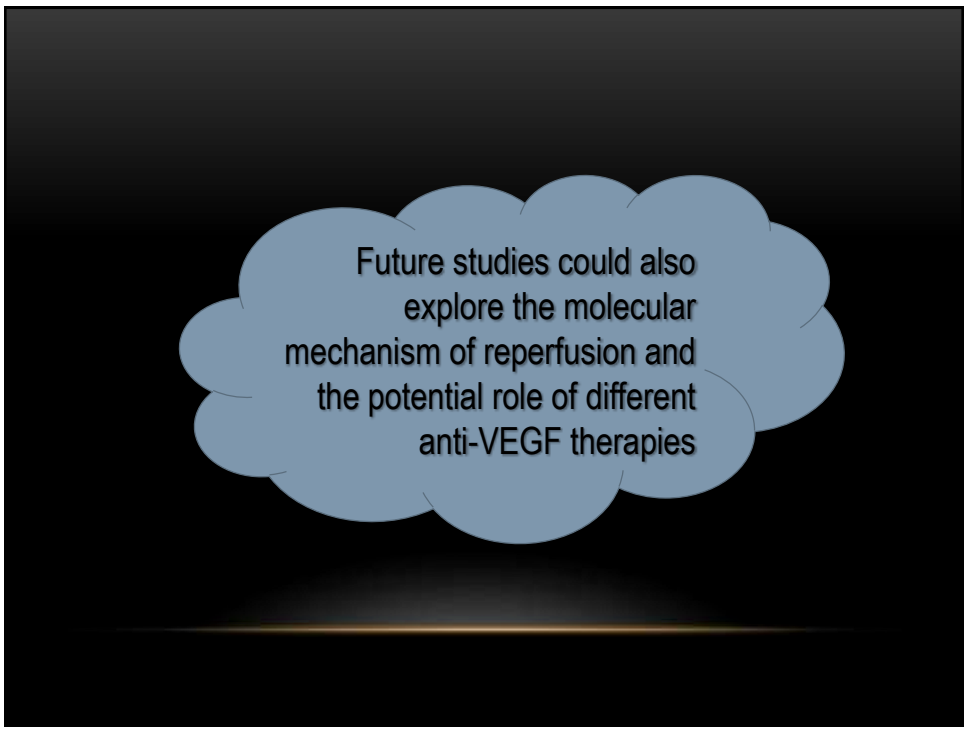
TAKE HOME MESSAGE

Treatment with anti-VEGF agents can be associated with reperfusion of areas of non perfusion.


Prospective studies evaluating the effect of anti-VEGF therapy on perfusion should incorporate correlations to macular thickness response and other imaging features in the study design.


Future studies could also explore the molecular mechanism of reperfusion and the potential role of different anti-VEGF therapies


Thank You